PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 February 2001 (08.02.01)	
International application No. PCT/IB00/00933	**Applicant's or agent's file reference** A088PCT
International filing date (day/month/year) 02 June 2000 (02.06.00)	**Priority date** (day/month/year) 04 June 1999 (04.06.99)
Applicant POLMAN, Chris	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 December 2000 (20.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
A088PCT		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/00933	02/06/2000	04/06/1999

International Patent Classification (IPC) or national classification and IPC
A61K31/425

Applicant
VERENIGING VOOR CHRISTELIJK ... et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/12/2000	27.07.2001

Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Toulacis, C Telephone No. +49 89 2399 8638

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/00933

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-9	as originally filed

Claims, No.:

1-14	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2-14 with regard to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 2-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The following International Preliminary Examination has been carried out on the assumption that the present application is fully entitled to its priority date as claimed.

III

Claims 2-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V

For the assessment of the present claims 2-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 1-14

(N) The use of rizulole in the treatment of multiple sclerosis (MS), is not disclosed in the documents cited in the search report (Art. 33(2) PCT).

(IS) The object of the present application is to provide additional treatments for MS which can treat the disease, minimize the effects of the disease, or slow the progression of the disease (description; page 2, lines 10-11).
Said object has been achieved by using rizulole. This is supported by measuring the change in spinal cord cross-sectional area by RMI scanning (description; page 7, line 27 to page 8, lines 13; page 9, table 1).
Document G. MCCREADY (ED.): "Rilutek might be tried for MS" MS PATHFINDER, June 1998 (1998-06); **(D1)**, however, clearly suggests the use of rizulole in MS which is similar in its damage characteristics to other nerve damaging diseases such as Parkinson's, Alzheimer's and ALS (lines 4-6); (Art. 33(3) PCT).

(IA) The industrial applicability of claim 1 is given.

VII

The various definitions of the invention given in independent claims 1, 2, 8, 11 and 13, are such that the claims as a whole are not clear and concise contrary to Art. 6 PCT in combination with Rule 6.4 a), b) and c) PCT.

General statements in the description which imply that the extent of protection may be expanded in some vague and imprecise way should be deleted (description, page 8, lines 14-18; Guidelines C-III, 4.3a PCT).

In the description of the present application (page 8, line 11), reference is made to Fig. 1. Said Figure, however, is missing from the documents as originally filed.

VIII

The expression "analogs, homologs or variants of rizulole having substantially the same activity and structure as rizulole" used throughout the description (e.g. page 3, lines 24-27; page 4, lines 2-3), is not clear (Art. 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
A088PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/ 00933	02/06/2000	04/06/1999

Applicant

VERENIGING VOOR CHRISTELIJK WETENSCHAPPELIKJK ONDE

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has be n furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF RILUZOLE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. Th applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant. [ ] Non of th figures.

   [ ] because th applicant failed to suggest a figure.

   [ ] because this figure better charact rizes th invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/00933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. MCCREADY (ED.): "Rilutek might be tried for MS" MS PATHFINDER, June 1998 (1998-06), XP002122163 abstract ---	1-14
P,X	N.F. KALKERS: "A pilot study of riluzole in primary progressive multiple sclerosis; effect on spinal cord atrophy on MRI" 9TH MEETING OF THE EUROPEAN NEUROLOGICAL SOCIETY, POSTER P419, 6 June 1999 (1999-06-06), XP002122164 abstract --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2000	06/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B. STANKOFF: "Neuroprotection and Central Nervous System myelination: New prospects for multiple sclerosis?" NEUROLOGY, vol. 52, no. 6, 12 April 1999 (1999-04-12), page A402 XP002122165 abstract	1-14
A	WO 93 17683 A (RHONE POULENC RORER SA) 16 September 1993 (1993-09-16) the whole document & EP 0 558 861 A (IBID.) 8 September 1993 (1993-09-08) cited in the application	1-14

INTERNATIONAL SEARCH REPORT

International application N .
PCT/IB 00/00933

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for th following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 2 to 14 are directed to a method of treatment of the human body, the search has been carried out, based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] Th additional search fees w re accompanied by the applicant's protest.

[ ] No protest accompanied th payment of additional search fees.

INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No
PCT/IB 00/00933

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9317683 A	16-09-1993	FR 2688138 A	10-09-1993
		AT 149833 T	15-03-1997
		AU 666150 B	01-02-1996
		AU 2948292 A	05-10-1993
		CA 2117466 A	16-09-1993
		CZ 9402120 A	15-12-1994
		DE 69218255 D	17-04-1997
		DE 69218255 T	11-09-1997
		DK 627919 T	12-05-1997
		EP 0558861 A	08-09-1993
		EP 0627919 A	14-12-1994
		ES 2098558 T	01-05-1997
		GR 3022797 T	30-06-1997
		HU 70946 A,B	28-11-1995
		IL 103493 A	23-07-1996
		JP 2713384 B	16-02-1998
		JP 7504655 T	25-05-1995
		KR 190296 B	01-06-1999
		MX 9206109 A	01-09-1993
		NO 943256 A	02-09-1994
		RU 2110260 C	10-05-1998
		SK 104794 A	10-05-1995
		US 5527814 A	18-06-1996
		ZA 9208213 A	30-04-1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/74676 A1

(51) International Patent Classification[7]: A61K 31/425

(21) International Application Number: PCT/IB00/00933

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99201788.9 4 June 1999 (04.06.1999) EP
60/174,328 4 January 2000 (04.01.2000) US

(71) Applicants *(for all designated States except US)*: **VERENIGING VOOR CHRISTELIJK WETENSCHAPPELIKJK ONDERWIJS** [NL/NL]; De Boelelaan 1105, NL-1081 HV Amsterdam (NL). **BIOGEN, INC.** [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **POLMAN, Chris** [DK/NL]; Ernst Casimirlaan 86, NL-2051 HE Overveen (NL).

(74) Agent: **FLYNN, Kerry, A.**; Biogen, Inc., 14 Cambridge Center, Cambridge, MA 02142 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/74676 A1

(54) Title: USE OF RILUZOLE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

(57) Abstract: Methods and compositions for the treatment of multiple sclerosis comprising riluzole (6-(trifluoromethoxy)-benzothiazolamine).

USE OF RILUZOLE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

The present invention relates to methods for treating multiple sclerosis and to methods of preparation of pharmaceutical compositions to be used for the treatment of multiple sclerosis.

Background

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). It is a major cause of disability, because in most patients the disease ultimately has a progressive course. In most patients, the progressive course of the disease manifests itself during or after a preceding phase of relapses and remissions (secondary progressive (SP) disease), whereas in a small percentage of patients (10-15%) the disease course is progressive from onset (primary progressive (PP) disease).
Most currently available treatments for multiple sclerosis are aimed at suppressing the inflammatory component of the disease. Their main clinical impact is on relapses whereas an effect on permanent disability is less well established. Patients with PPMS show less inflammatory activity, which is one of the reasons why they are frequently excluded from treatment trials, despite clear clinical progression. Recent evidence sugggests that axonal loss may occur earlier in the disease course of MS than previously anticipated; it may be the pathologic correlate of irreversible disability.

MS is frequently characterized by plaques or lesions of demyelination in the nerve fibers of the brain and spinal cord. Demyelination causes multiple and varied neurologic symptoms and signs, usually with relapses and exacerbations.

The clinical course of MS is highly variable and unpredictable, with many patients experiencing acute episodes of exacerbations, followed by periods of remission. The disease progresses at various paces to a chronic, degenerative condition. Frequently, a diagnosis of MS may not be made for many years after the onset of symptoms because the symptoms can be variable, sporadic, and similar to those associated with other disorders. As the disease progresses, patients are frequently unable to remain fully ambulatory, and their functional systems steadily decline. The most severe cases of MS are characterized by paralysis or even death.

MS may occur in several forms classified as primary progressive, relapsing-remitting, and secondary progressive, depending on the pathophysiology, progression and severity of the symptoms.

There are several theories about the causes of MS, however, the precise causes of MS are not yet known. Research to date has indicated that the etiology of MS may in fact be related to a combination of factors, such as autoimmunity, environmental, viral and genetic factors.

Riluzole (6-(trifluromethoxy)-2-benzothiazolamine) is described in European Patent 50,511 and US Patent 4,370,338. Its use in the treatment of motor nerve diseases is described in European Patent 558,861. Riluzole is produced by Rhone-Poulenc Rorer (RPR) and is used for the treatment of amyotrophic lateral sclerosis (ALS), a disease unrelated to MS.

There remains a need to identify additional treatments for MS which can treat the disease, minimize the effects of the disease, or slow the progression of the disease.

Summary of the invention

The present invention results from the novel and surprising discovery that riluzole is useful in the preparation of pharmaceutical compositions for the treatment of all forms of multiple sclerosis. Thus, in various embodiments discussed herein, the presently claimed invention relates to the use of riluzole for preparing a pharmaceutical composition suitable for the treatment of multiple sclerosis, and methods for the treatment of multiple sclerosis, comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of riluzole. The methods of treatment and methods of preparing pharmaceutical compositions disclosed herein may include not only riluzole, but also riluzole in combination with a pharmaceutical composition comprises a pharmaceutically effective carrier.

In yet other embodiments, the claimed invention relates to pharmaceutical compositions comprising a therapeutically or prophylactically effective amount of riluzole in combination with an additional agent having pharmaceutical properties. The additional agent can be any agent deemed useful by one skilled in the art in treating MS, or ameliorating or inhibiting the symptoms of MS, including, but not limited to, Type I interferons such as interferon beta - 1b, copaxone, interferon beta-1a, muscle relaxants, anti-depressants, or immunosuppressants. Additionally, the claimed invention relates to

methods of treatment of patients suffering from MS by administering an effective amount of such combinations to patient in need thereof.

In certain embodiments, the claimed compositions are administered in an amount of between about 10 and about 500 mg per day., more preferably, between about 50 and about 250 mg per day. Similarly, the preferred methods comprise administering these same dosages.

In yet other embodiments, the claimed invention relates to methods of inhibiting, minimizing or delaying the development of spinal cord atrophy associated with MS by administering an effective amount of riluzole, or riluzole in combination with a second agent as discussed above. The presently claimed invention relates to all types of MS, including those known, and types yet to be categorized. In various embodiments, the claims relate to methods for the treatment of a patient suffering from primary progressive MS, secondary progressive MS, and or relapsing-remitting MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Reference will now be made in detail to the present preferred embodiments of the invention, examples of which are set forth herein.

Discussion:

As mentioned above, most currently available treatments for MS are aimed at suppressing the inflammatory component of the disease. Their main clinical impact is on relapses, whereas an effect on permanent disability has so far been less well established. The claimed invention relates to the use of riluzole in the treatment of multiple sclerosis. Riluzole, as used herein, refers to (6-(triflurомethoxy)-2-benzothiazolamine) as described in European Patent 50,511 and US Patent 4,370,338, as well as all analogs, homologs or variants thereof which have substantially the same activity and structure as riluzole.

The compositions of the invention can be made by methods known to those skilled in the art. Simply stated, riluzole can be prepared by the action of potassium thiocyanate and bromine on 4-triflouromethoxy-aniline in acetic acid medium. Preferred methods of preparation can be determined by those skilled in the art depending upon the desired economics and simplicity of process.

As used herein, the claimed pharmaceutical compositions may comprise a therapeutically effective amount of 6-(triflurомethoxy)-2-benzothiazoloamine), its analogs, homologs, variants or salts thereof. Specifically, the present invention encompasses pharmaceutical compositions comprising pharmaceutically acceptable salts derived from inorganic or organic acids and bases.

The claimed methods can be used in the treatment of patients suffering from MS at any time in the progression of the disease, and may be used to treat patients suffering from primary progressive MS, secondary progressive MS, and /or relapsing remitting MS. It is preferred to use the claimed methods for the treatment of primary progressive MS.

The claimed invention in certain embodiments may act through the inhibition of glutamate transmission, an excitotoxin participating in the process of neuronal damage.

In various embodiments the claimed methods can encompass the administration of a therapeutically effective amount of riluzole alone, or in combination with another therapeutic or prophylactic agent. By administration in combination, it is meant that riluzole can be administered either substantially simultaneously with the second agent, or that the second agent can be administered in a stepwise fashion with riluzole. Thus, in various embodiments, depending on the particular treatment regime chosen by the physician, one may administer riluzole at the same time as the second agent, or in other embodiments, riluzole and the second agent can be administered hours, days, or possibly even weeks apart. The desired treatment regime can be easily determined by one skilled in the art depending upon the particulars of the patient being treated, and the desired outcome.

Any therapeutic or prophylactic agent useful in the treatment of MS or any of its associated symptoms may be used as the second agent according to this invention. In preferred embodiments, the second agent is selected from the type I interferons, more preferably, interferon beta - 1a. Additionally, however, other second agents can be used in the claimed invention, including, but not limited to steroids, pain relievers, muscle relaxants, immunosuppressants and copaxone .

The compounds of the present invention may be formulated into pharmaceutical compositions that may be administered orally, parenterally, such as, for example, retrobulbar administration, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes

subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions of this invention comprise any of the compounds of the present invention, or pharmaceutically acceptable derivatives thereof, together with any pharmaceutically acceptable carrier. The term "carrier" as used herein includes acceptable adjuvants and vehicles. Pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

According to this invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation through the use of a nebulizer, a dry powder inhaler or a metered dose inhaler Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline,

employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, and the particular mode of administration. It should be understood, however, that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of active ingredient may also depend upon the therapeutic or prophylactic agent, if any, with which the ingredient is co-administered.

The dosage and dose rate of the compounds of this invention effective to prevent, suppress or inhibit cell adhesion will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the judgment of the treating physician. Dosage levels of between about 10 and about 500 mg per day, preferably between about 25 to 250 mg per day, and most preferably, between about 100 to 150 mg per day of riluzole are useful.

Example 1:

We selected 9 women and 7 men (aged 30-66 years) with documented progression during the 24 months before inclusion, from a natural history study. Kurtzke's EDSS scores were between 3.0 (inclusive) and 7.5 (inclusive). All adverse events were documented; safety lab consisted of serum transaminases (monthly for 3 months and every 3 months thereafter) and hematology (CBC and differential every 6 months) after the start of treatment. The study was approved by the hospital ethics committee, and all patients gave informed consent. During the first year no specific treatment was given; during the second year all patients were treated with riluzole (2 x 50 mg daily). MRI scanning consisted of a 6-monthly inversion prepared 3D gradient echo sequence of the cervical cord, and yearly T1- and T2- weighted spin-echo sequences of the brain. The main efficacy parameter was the change in spinal cord cross- sectional area, obtained from 10 contiguous 3-mm axial slices perpendicular to the cord above the center of the C2-C3; the coefficient of variation

for this method in our hands was 1.3%. Scans were analysed in a randomized and blinded fashion.

Results

Two patients discontinued treatment because of side effects (headache in one, increase in spasticity in the other). Five patients needed intermittent reduction in dosage of study drug. In 14 patients who took medication for over three months, medically severe adverse effects were not observed. Adequate MRI data could not be obtained at multiple time points in one patient, while five others had one missing data point. As shown in Table 1 a clear reduction (2%) in cord area (**p=0.59**) in the first year was found, and an increase in T1 and T2 lesion loads, as expected. In the second year we saw a stabilisation in cord diameter (-0.15%), see Figure 1. The increase in T2 lesion load in the brain did not alter much under treatment, but the accumulation of hypointense lesion showed a trend towards reduction (**p=0.66**). No effect on EDSS score was seen.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

Table 1: Baseline data for spinal cord area, T1 and T2 lesion load, the increase in year without and with treatment and with respective 95% confidence interval (CI)

MRI parameter	Baseline	□ 0-1 yr	□ 1-2-yr	difference □ 0-1 yr versus □ 1-2-yr
Spinal cord area[1]	66.7 mm^2	-1.3 mm^2 (- 2%) CI: -4.5 to 3.5%	-0.2 mm^2 (-0.15%) CI: -4.0 to 2.4%	-1.5 mm^2 (-2.15%) CI: -4.8 to 4.9 %
T1 lesion load[2]	271.5 mm^3 (0.0-7032.0)	median 15% mean 27% CI: -9.3 to 63%	median 6% mean 24% CI: -2.1 to 51%	median 24% mean 53% CI: 2.1 to 104%
T2 lesion load[2]	2160.0 mm^3 (513.0-32892.0)	median: 7% mean 13%: CI: -3.5 to 30%	median: 10% mean 12% CI: -3.8 to 29%	median 21.6% mean 28 % CI: -2.1 to 54%

[1] mean in mm^2 (SD); [2] median (range)

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What is claimed is:

1. The use of riluzole for preparing a pharmaceutical composition suitable for the treatment of multiple sclerosis.

2. Method for the treatment of multiple sclerosis, comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of riluzole.

3. The method of claim 2 wherein said pharmaceutical composition comprises a pharmaceutically effective carrier.

4. The method of claim 2 wherein said pharmaceutical composition further comprises a therapeutically or prophylactically effective amount of an additional agent.

5. The method of claim 4 wherein said additional agent is selected from the group consisting of interferon beta -1a, interferon beta -1b, or copaxone.

6. Method according to claim 2 wherein said composition is administered in an amount of between about 10 and about 500 mg per day.

7. The method of claim 6 wherein said composition is administered in an amount of between about 50 and about 250 mg per day.

8. A method for treating a patient suffering from multiple sclerosis comprising the step of administering a pharmaceutical composition comprising riluzole in an amount effective to inhibit, minimize or delay the development of spinal cord atrophy associated with MS.

9. The method of claim 8 wherein said pharmaceutical composition further comprises a therapeutically or prophylactically effective amount of an additional agent selected from the group consisting of intereferon beta -1b, interferon beta -1a, or copaxone.

10. A method for the treatment of a patient suffering from MS comprising the steps of administering to said patient:

a. a therapeutically effective amount of a pharmaceutical composition comprising riuluzole;

b. a therapeutically effective amount of a pharmaceutical composition selected from the group consisting of interferon beta -1b, interferon beta -1a, or copaxone.

11. A method for the treatment of a patient suffering from primary progressive MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

12. The method of claim 11 further comprising the administration of a therapeutically effective amount of interferon beta -1b, copaxone or interferon beta-1a.

13. A method for the treatment of a patient suffering from secondary-progressive MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

14. A method for the treatment of a patient suffering from relapsing-remitting MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 00/00933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. MCCREADY (ED.): "Rilutek might be tried for MS" MS PATHFINDER, June 1998 (1998-06), XP002122163 abstract ---	1-14
P,X	N.F. KALKERS: "A pilot study of riluzole in primary progressive multiple sclerosis; effect on spinal cord atrophy on MRI" 9TH MEETING OF THE EUROPEAN NEUROLOGICAL SOCIETY, POSTER P419, 6 June 1999 (1999-06-06), XP002122164 abstract --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2000	06/10/2000

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 00/00933

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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...formation on patent family members

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